

Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors

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On behalf of the HABITS Study Group

- Background** Hormone replacement therapy (HT) is known to increase the risk of breast cancer in healthy women, but its effect on breast cancer risk in breast cancer survivors is less clear. The randomized HABITS study, which compared HT for menopausal symptoms with best management without hormones among women with previously treated breast cancer, was stopped early due to suspicions of an increased risk of new breast cancer events following HT. We present results after extended follow-up.
- Methods** HABITS was a randomized, non-placebo-controlled noninferiority trial that aimed to be at a power of 80% to detect a 36% increase in the hazard ratio (HR) for a new breast cancer event following HT. Cox models were used to estimate relative risks of a breast cancer event, the maximum likelihood method was used to calculate 95% confidence intervals (CIs), and χ^2 tests were used to assess statistical significance, with all *P* values based on two-sided tests. The absolute risk of a new breast cancer event was estimated with the cumulative incidence function. Most patients who received HT were prescribed continuous combined or sequential estradiol hemihydrate and norethisterone.
- Results** Of the 447 women randomly assigned, 442 could be followed for a median of 4 years. Thirty-nine of the 221 women in the HT arm and 17 of the 221 women in the control arm experienced a new breast cancer event (HR = 2.4, 95% CI = 1.3 to 4.2). Cumulative incidences at 5 years were 22.2% in the HT arm and 8.0% in the control arm. By the end of follow-up, six women in the HT arm had died of breast cancer and six were alive with distant metastases. In the control arm, five women had died of breast cancer and four had metastatic breast cancer (*P* = .51, log-rank test).
- Conclusion** After extended follow-up, there was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT.
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Endogenous estrogen and progesterone play central roles in breast development and breast cancer. There is substantial evidence from observational studies that hormone replacement therapy (HT) increases the risk of breast cancer in healthy women (1). For this reason, HT has been considered to be contraindicated for breast cancer survivors. However, compelling reasons have arisen for an empirical test of whether HT is safe for climacteric symptoms in women with previously treated breast cancer. First, there are now more breast cancer survivors with climacteric symptoms due to increased incidence of breast cancer and improved survival times after treatment. Second, many current systemic cancer treatments induce early menopause and climacteric symptoms that are difficult to manage by nonhormonal means. Third, it is possible that the

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CONTEXT AND CAVEATS

Prior knowledge

The HABITS trial, on the effect of hormone replacement therapy (HT) on breast cancer risk among breast cancer survivors, was stopped in December 2003 after two large studies reported that HT increases risk of breast cancer among healthy women. In 2004, preliminary results from a median follow-up of 2 years were reported.

Study design

HABITS was a randomized, open-label noninferiority trial in which 447 Scandinavian women were randomly assigned to either HT (most often, to continuous combined or sequential estradiol hemihydrate and norethisterone) or to best symptomatic treatment without hormones.

Contribution

A total of 442 women could be followed for a median of 4 years. Women in the HT arm experienced new breast cancer events more than twice as often as women in the control arm (39 out of 221 vs 17 out of 221; hazard ratio = 2.4, 95% confidence interval = 1.3 to 4.2). The cumulative incidence of a new breast cancer event at 5 years was estimated at 22.2% for the HT arm and at 8.0% for the control arm.

Implications

Clinicians and their patients should weigh the benefits of use of HT for postmenopausal symptoms with the increased risk for new breast cancer events.

Limitations

The time at which the trial was terminated, certain characteristics of the patient population, and the types of HT used each could influence the degree to which use of HT increases breast cancer risk. The study was not placebo controlled, and some judgments about disease recurrence can be subjective.

mechanism whereby HT induces and promotes tumor growth in healthy women may be different from its ability to promote the growth of microdeposits of tumor cells in breast cancer survivors.

These questions regarding the potential benefits and dangers of HT in women previously treated for breast cancer have triggered a series of observational studies and analyses of clinical case series whose results seemed reassuring in general in that they found no increased risk of breast cancer recurrence following HT. Indeed, a meta-analysis of eight observational studies (2) that included 3710 women (among whom the HT users had taken HT for a mean of 28 months and were followed for a mean of 57.1 months) showed a relative risk (RR) of breast cancer recurrence of 0.64 (95% confidence interval [CI] = 0.50 to 0.82) in users compared with nonusers (2). However, to date, only three small randomized studies have been initiated to address the safety of conventional HT in women with a previous breast cancer (3–5). During the course of these studies, further evidence of the association between HT and breast cancer risk in women without a previous breast cancer was provided by data from a large randomized trial (6) and a large observational study (7). Specifically, the prospectively randomized Women's Health Initiative study (6) found an RR of 1.26 (95% CI = 1.0 to 1.59) for breast cancer in HT users after a mean of 5.2 years

of follow-up. Current users of HT at recruitment into the observational Million Women Study (7) also had increased risk of breast cancer compared with nonusers (RR = 1.66, 95% CI = 1.58 to 1.75).

The HABITS (Hormonal Replacement After Breast Cancer—Is it Safe?) trial was initiated alongside two similar studies (3–5) to evaluate in a prospective randomized trial whether HT for menopausal symptoms is safe in women with a previously treated breast cancer. The goal of this noninferiority trial was to recruit 1300 women to exclude the possibility that 2 years of HT conferred a relative risk of a new breast cancer event that exceeded 1.36, as compared with best symptomatic treatment without hormones. At the time that the protocol was designed and the study centers were recruited, it was felt that the only realistic way to reach the study goals was to allow a pragmatic choice of type of HT, so a variety of types of HT were allowed, depending on the choice of the patient and her physician(s).

The HABITS trial was initiated in May 1997. The Data Monitoring and Safety Committee (DMSC) for the HABITS trial carried out a planned interim analysis designed to detect a harmful effect of HT in March 2001. In February 2002, the organizers of the HABITS trial and of a similar trial in Stockholm, Sweden (5), agreed to pool safety analyses and to use a joint DMSC. The joint DMSC performed two interim analyses—also, designed only to detect a harmful effect—with pooled data from the HABITS and Stockholm studies in December 2002 and October 2003. Following protocol, the DMSC discussed its findings with the steering committees of the HABITS and Stockholm studies when, in October 2003, the combined estimate of the hazard ratio (HR) for recurrence with HT compared with recurrence without HT reached 1.8 (95% CI = 1.03 to 3.1) and was thus statistically significantly larger than 1.0. However, there was a statistically significant heterogeneity between the studies, with HRs of 3.3 in the HABITS study and 0.82 in the Stockholm study ($P = .02$) (4,5). The DMSC recommended that the HABITS trial stop and that the Stockholm investigators consider the consequences of the safety analysis for their trial.

The HABITS steering committee terminated its study in December 2003 (4). At this time, 447 women had been recruited and randomly assigned. When preliminary results based on a median follow-up of 2 years were reported (4), 33 breast cancer events had occurred and the hazard ratio had reached 3.5 (95% CI = 1.5 to 7.4). Here, we report results from a median follow-up of 4 years and a total of 56 breast cancer events.

Subjects and Methods

Subjects and Recruitment

Women were eligible if they had previously completed primary treatment for breast cancer, including a complete removal of the tumor and axillary surgery, radiotherapy, and chemotherapy as stipulated by the local treatment guidelines. Concomitant treatment with adjuvant tamoxifen, but not with aromatase inhibitors, was allowed. The protocol stipulated that the tumor should be a histopathologically confirmed stage 0–2 breast cancer with less than four involved axillary lymph nodes. The participants were required to be free of recurrence, to have no other cancer or serious disease, and to have no other contraindications to HT. Furthermore, it was

required that participating women have menopausal symptoms that both they and their doctors deemed to need treatment. Recruitment began in May 1997 and ended in December 2003, when the trial was stopped.

Local networks of oncologists, surgeons, and gynecologists recruited, randomly assigned, and followed the participants. Centers from the Scandinavian Breast Group (SBG), the International Breast Cancer Study Group (IBCSG), and the European Organization for Research and Treatment of Cancer (EORTC) participated in the study under the umbrella of the Breast International Group (BIG). Random assignment was done by telephone, mail, or fax to the study headquarters, which was located separately from the clinics at the Regional Oncological Center in Uppsala, Sweden. The allocation scheme was computer generated in blocks of eight and was stratified by participating center, use of HT before diagnosis of the original breast cancer, and treatment with tamoxifen. The block size was unknown to the participating clinicians. Full oral informed consent was required. The study was approved by the local ethics committees at each participating center. The full trial protocol is available at <http://www.roc.se>. The study was registered prospectively with *The Lancet* in 1997 (registry number 97/PRT/23).

Interventions

Women were randomly assigned to receive either HT or best symptomatic management without hormones. Acupuncture for relief of symptoms (8) was allowed, but the synthetic steroid tibolone was not. Choice of the specific type of HT was directed by local practice. If there was no preferred specific therapy in a particular center, a sequential estrogen–progestagen combination was prescribed for women with an intact uterus whose last menstruation was within the past 2 years. A continuous combined regimen was prescribed for women 2 or more years past menopause. Medium-potency estrogens alone (ie, estrogens effective in treating hot flashes, which have higher potency than those used to stimulate urogenital mucosa but substantially lower potency than those used in oral contraceptives) were prescribed for women who had undergone hysterectomy. HT was given for 2 years in the HT arm. The majority of centers prescribed a sequential or continuously combined regimen of estradiol hemihydrate (E2) and norethisterone acetate (NETA) for women with an intact uterus or estradiol for women who had undergone hysterectomy. This was an open-label study. After 2 years, patients were asked to stop treatment. If serious withdrawal symptoms occurred, they were prescribed gradually decreased dosages over a 6- to 12-month period.

Follow-up and Endpoints

The protocol recommended that participants be followed by a breast cancer specialist at least twice yearly for the first 3 years after random assignment and continue to be followed by a breast cancer specialist at least annually for at least 5 years in total. We recommended that the patients receive mammograms every 12–24 months or participate in routine mammographic screening with target intervals of 18–24 months. Participants were also required to be seen by a gynecologist every year. New breast cancer events, any other new cancer, compliance, and side effects of treatment were recorded prospectively.

The main endpoint for this study was the first occurrence of any new breast cancer event, including contralateral breast cancer. Death from breast cancer was considered to be an event, provided that it was not preceded by an overt clinical breast cancer event. Between March 2005 and May 2006, all participating physicians checked the medical records of all randomly assigned patients to ensure that the data reported to the study headquarters at the time of randomization were accurate, to report further data from the treatment of the initial breast cancer, to report on compliance and total time on HT, and to verify follow-up status.

A serious adverse event was defined as any undesirable reaction to a drug or treatment that occurred within 8 weeks of stopping any study intervention and that resulted in death, a life-threatening condition, hospitalization, persistent disability, unexpected severe toxicity, congenital anomaly or birth defect, second cancer, or another health problem requiring medical intervention. Serious adverse events were to be reported within 24 hours to the study headquarters.

Statistical Methods

The study was designed as a noninferiority trial (9). Under the assumption that the benefits of HT may be outweighed by some risk, but not by risk exceeding one and a third times the risk without HT, the study was designed to have a power of 80% to detect at least a HR of 1.36 or higher for a new breast cancer event following random assignment to HT as compared with best symptomatic treatment without hormones. For this power, a total sample size of 1300 women was needed for a one-sided log-rank test with a statistical significance level of 5% (at HR = 1.36) assuming a median follow-up of 5 years and a 20% cumulative incidence of new breast cancer events over 5 years in the non-HT group.

In the present report, all analyses were performed according to intention-to-treat principles. The hazard ratio with a 95% confidence interval derived from Cox proportional models (10) was used as the measure of relative risk when comparing the number of events in patients randomly assigned to HT with those randomly assigned to the non-HT group. The proportional hazards assumption was judged by comparing Kaplan–Meier plots of survival against $\log(\log(\text{survival}))$ for each group of randomly assigned patients and found to hold. The confidence intervals were estimated with the maximum likelihood method, and *P* values for hazard ratios were derived from χ^2 tests. In the adjusted models, age was used as a continuous variable and binary variables (yes vs no) were used for hormone receptor positivity (either a positive estrogen receptor or progesterone receptor status or both), ongoing treatment with tamoxifen, prior treatment with HT before primary breast cancer diagnosis, and presence of axillary metastases. The absolute risk of a new breast cancer event was estimated with the cumulative incidence function, with non-breast cancer death as competing event (11). A statistical significance level of 5% (two-sided tests) was used throughout.

Results

We previously reported on follow-up of 345 women with at least one follow-up record for all 434 women registered as of September 2003

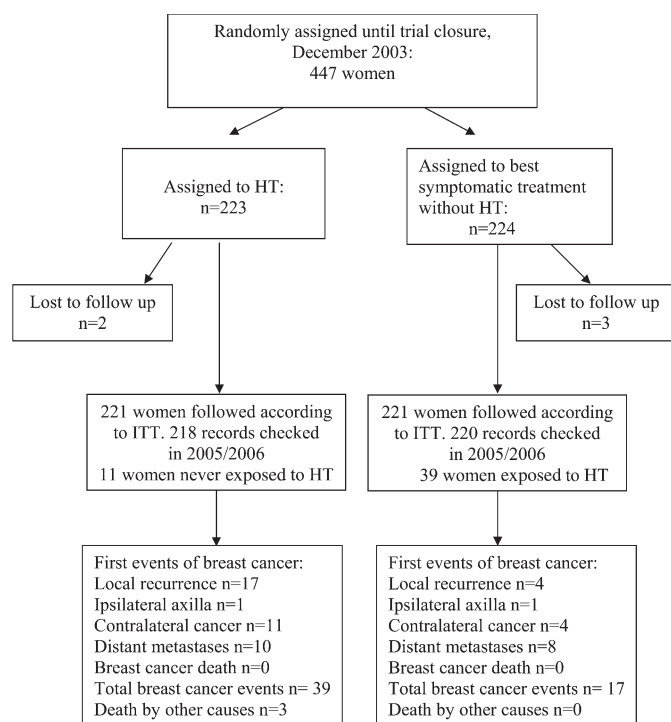


Figure 1. Diagram of patient flow in the HABITS trial. HT = hormonal replacement therapy; ITT = intention to treat.

(4). At that time, 26 women in the HT arm and seven in the non-HT arm had experienced a new breast cancer event. The present report includes the 442 women for whom follow-up data were available out of the 447 women who were included in the HABITS trial at its termination on December 17, 2003 (Figure 1). As of December 2006, after a median follow-up of 4 years, there were a total of 39 breast cancer events in the HT arm and 17 in the non-HT arm.

Baseline Characteristics

The baseline characteristics of HABITS participants were similar in the two arms (Table 1). The only notable difference was that more women in the HT arm than the non-HT arm had had hormone receptor–positive cancer (62.3% vs 54.5%). The ages of the women at random assignment varied widely in both arms, as did the time interval between the first diagnosis of breast cancer and random assignment. However, for 80% of the women in both arms, the time between first diagnosis and random assignment was between 7 months and approximately 8 years. A majority of the women were node negative when initially diagnosed. About half of the women were taking HT before diagnosis and treatment of breast cancer, but only 33.5% were taking tamoxifen at the time of random assignment (Table 1).

Because the study was not blinded, we were concerned that more intensive follow-up in women who were prescribed HT could introduce an information bias. However, the number of follow-up physician visits was similar in both groups (Table 1).

Exposure to HT

The monitoring of all medical records in 2005–2006 gave complete information on the type of HT treatment for 246 women (203 in

Table 1. Baseline characteristics in women with follow-up by randomization arm*

Characteristic	HT arm	Non-HT arm
No. with follow-up	221	221
Follow-up in years, median (range)	4.1 (0.01–7.8)	4.0 (0.2–7.7)
Time in years between primary treatment and randomization, median (range)	2.1 (0.1–23.2)	2.2 (0.1–26.5)
Age in years, mean (range)	55.6 (42–75)	54.8 (38–74)
Node positive, No. (%)	44 (19.7)	42 (18.8)
Hormone receptor positive, No. (%)	139 (62.3)	122 (54.5)
Hormone receptor status unknown, No. (%)	64 (28.7)	75 (33.5)
Breast preserved, No. (%)	127 (57.0)	126 (56.3)
On HT before diagnosis, No. (%)	115 (51.6)	115 (51.3)
On adjuvant tamoxifen at randomization, No. (%)	75 (33.6)	75 (33.5)
Follow-up clinic visits for breast cancer, median	6	6

* HT = hormone replacement therapy (HT arm designates those randomized to HT but not necessarily compliant).

the HT arm and 43 in the non-HT arm) and on the duration of HT treatment for 238 women (199 in the HT arm and 39 in the non-HT arm; Table 2). Most of the women who received HT were prescribed combined regimens. Of the 119 on a continuously combined regimen (ie, 100 compliant women from the HT arm and 19 noncompliant women from the control arm), 72 women were given 2 mg E2 and 1 mg NETA (Kliogest) daily, and 15 were given 1 mg E2 and 0.5 mg NETA (Activelle) daily. Of the 61 on sequential regimens (53 from the HT arm and eight from the control arm), 38 women were prescribed a 28-day cycle with 2 mg E2 on days 1–12, 2 mg E2 plus 1 mg NETA on days 13–22, and 1 mg E2 on days 23–38 (Trisekvens). For the 54 women exposed to estrogen only (47 from the HT arm and seven from the control arm), 20 women took 1–2 mg E2 (Estrafem) daily and 10 took 0.625 or 1.25 mg conjugated estrogens (Compremin) daily. All other preparations were taken by fewer than 10 women each.

Eleven women in the HT arm did not receive any HT, whereas 43 in the non-HT arm received HT, about one-third of whom also changed the type of HT during the study (Table 2). The median duration of HT use was around 2 years in both randomization groups, but there was a wide range of exposure times (Table 2). However, of those who used HT during the trial, 90% used it for 4 years or less and only 10% used it for less than 6 months. Among the 199 women in the HT arm who took HT and for whom we had complete information about HT treatment times, 64 (32%) changed medication once and 14 (7%) changed it two or more times (Table 2). Although some women who were on HT when the trial was stopped continued taking it after the trial closure in 2003, no women without HT started taking it after the trial ended.

Risk of a New Breast Cancer Event

Thirty-nine women in the HT arm and 17 in the non-HT arm experienced one or more breast cancer events (Figure 1). The majority of first events in the HT arm were local recurrences or contralateral breast cancers. By contrast, in the non-HT arm, similar numbers of women had local recurrences or new breast cancers as had distant

Table 2. Exposure to different types of hormone replacement therapy preparations and times (months) of exposure by randomization arm in all women with follow-up*

HT exposure	HT arm (n = 221)	Non-HT arm (n = 221)
Never exposed, No.	11	178
Exposed, No.†	210	43
Median time (months) exposed (min–max)	23 (0–80)	23 (1–62)
HT preparation, No. (median)/min–max		
Continuously combined	100 (24)/0–80	19 (22)/3–62
Sequential	53 (23)/0–68	8 (14)/2–46
Estrogen only	47 (20)/1–70	7 (30)/1–48
Other	3 (15)/12–30	9 (30)/12–35
Unknown type of preparation	7	0
HT regimen changed once, No.	64	11
Changed HT regimen two or more times, No.	14	3

* HT = hormone replacement therapy; min = minimum; max = maximum.

† The median and min–max exposure times are derived from those with full information on exposure times (199 in the HT arm and 39 in the non-HT arm).

metastases. The absolute number of distant metastases as first event was similar in the two arms (Figure 1).

All women in the HT arm who developed a breast cancer event had been exposed to HT. Five of the women with a breast cancer event in the non-HT arm had also taken HT after random assignment. Nineteen women in the HT arm had a new breast cancer event after the 2-year follow-up period (when the treatment should have stopped according to protocol). Nine of these women had continued to use HT until the time of the event, and one had exposure until 4 months before the event.

Table 3 shows the hazard ratios for a new breast cancer event for women randomly assigned to HT vs no HT in this trial. Both the crude hazard ratio and the hazard ratio adjusted for use of HT before diagnosis of the original breast cancer, use of tamoxifen, and hormone receptor status show a statistically significantly elevated risk of a breast cancer event in the HT arm (HR = 2.4 [95% CI = 1.3 to 4.2] and HR = 2.2 [95% CI = 1.0 to 5.1] for the crude and adjusted models, respectively). The subset analyses stratified by HT use before diagnosis, use of tamoxifen, hormone receptor status, and lymph node status at primary treatment for breast cancer did not provide clear indications of effect modification or interaction. The only notable difference between strata was for tamoxifen use, with a higher risk among women who were using tamoxifen at the start of the trial compared with women who were not on tamoxifen at the time of random assignment (HR = 4.7 [95% CI = 1.4 to 16.2] vs HR = 1.9 [95% CI = 1.0 to 3.6]). However, the confidence interval for women on tamoxifen was wide, and there was no clear statistical evidence that tamoxifen modifies the effect of HT (the *P* value for interaction between HT and tamoxifen use was .11).

The cumulative incidences of a new breast cancer event at 2 years were 9.5% (95% CI = 5.5% to 13.5%) in the HT arm and 3.8% (95% CI = 1.2% to 6.4%) in the non-HT arm. The corresponding estimates at 5 years were 22.2% (95% CI = 15.6% to 28.7%) in the HT arm and 8.0% (95% CI = 3.8% to 12.3%) in the non-HT arm. The absolute differences between the arms were thus 5.7% (95%

Table 3. HRs with 95% CIs for risk of a new breast cancer event in the hormone replacement therapy group vs the non-hormone replacement therapy group according to intention to treat*,†

Characteristic	No. of events (No. of women in subset)	HR (95% CI)	<i>P</i> value‡ (χ^2)
All women	56 (442)	2.4 (1.3 to 4.2)	.003
All women, adjusted	52 (416)	2.2 (1.0 to 5.1)	.013
Hormone receptor positive	37 (268)	2.6 (1.3 to 5.4)	.009
Hormone receptor negative	19 (174)	1.8 (0.7 to 4.8)	.205
Tamoxifen	18 (153)	4.7 (1.4 to 16.2)	.015
No tamoxifen	38 (289)	1.9 (1.0 to 3.6)	.067
HT before diagnosis	26 (230)	2.3 (1.0 to 5.3)	.049
No HT before diagnosis	26 (186)	2.2 (1.0 to 5.1)	.061
Node negative	30 (282)	2.4 (1.1 to 5.4)	.026
Node positive	18 (110)	2.3 (0.8 to 6.4)	.117

* HR = hazard ratio; CI = confidence interval; HT = hormone replacement therapy.

† The adjusted model adjusts for hormone receptor status, nodal status at primary diagnosis, presence or absence of tamoxifen treatment, and exposure to HT before first breast cancer diagnosis.

‡ All *P* values are based on two-sided tests.

CI = 3.5% to 7.9%) at 2 years and 14.2% (95% CI = 10.9% to 17.5%) at 5 years. The cumulative incidence curves (Figure 2) show that the curves began to separate between 1 and 2 years of follow-up.

Risk Associated With Different Regimens

In a model of risk of a new breast cancer event among the women assigned to HT by type of HT, using continuously combined regimens as a reference category, we found no differences in risk across the main categories of HT use (Table 4). However, the subsets were small and both the statistical power and precision (as illustrated by the wide confidence intervals) were limited. A multivariable analysis that included age at random assignment, nodal

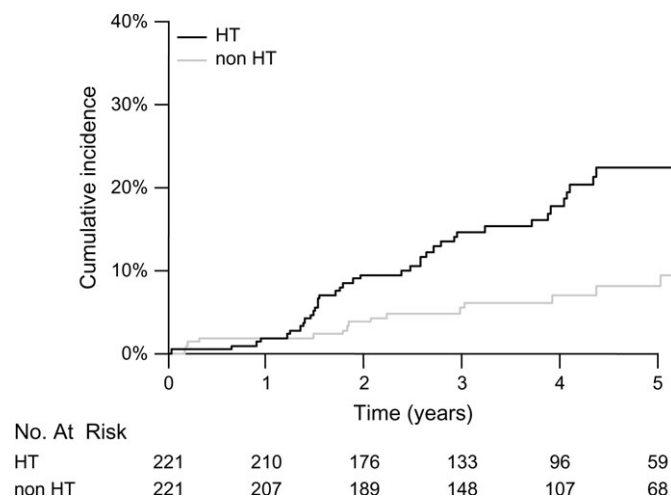


Figure 2. Cumulative incidence to first breast cancer event by intention to treat. Deaths by causes other than breast cancer are treated as competing events. There were 39 events in the HT arm and 17 in the non-HT arm. HT = hormonal replacement therapy.

Table 4. HRs with 95% CIs for any breast cancer event*

Type of preparation (No. exposed)	HR (95% CI)
Continuously combined (100)	1.0 (reference)
Sequential (53)	1.4 (0.6 to 2.9)
Estrogen (47)	1.4 (0.6 to 3.1)
Other (3)	4.3 (0.6 to 33.0)

* HR = hazard ratio; CI = confidence interval. This unadjusted analysis was restricted to the hormone replacement therapy arm, with 221 women and 39 events. Women exposed to the continuously combined regimen were used as the reference group.

status at primary diagnosis, and the use of tamoxifen during the trial did not alter the pattern seen in Table 4. Exposure to estrogen alone yielded a HR of 1.4 (95% CI = 0.55 to 3.3) as compared with exposure to a continuously combined regimen.

Distant Metastasis-Free and Overall Survival

By the end of follow-up, six women from the HT group had died of breast cancer and six were alive with distant metastases. For the non-HT group, five women had died of breast cancer and four were alive with distant metastases. The difference in distant metastasis-free survival was not statistically significant ($P = .51$, log-rank test). Three women in the HT arm died of causes other than breast cancer, compared with none in the non-HT arm.

Serious Adverse Events

Eight serious adverse events were reported in the HT arm and five in the non-HT arm. However, one of the serious adverse events in the HT arm, a primary lung cancer, was deemed to have little probability of being related to the HT medication or any other trial intervention, and two other reported events, one thrombophlebitis and one basal cell carcinoma of the skin, did not fulfill the criteria for serious adverse events. Therefore, an equal number of serious adverse events occurred in the two arms. The other events reported in the HT arm were one instance each of deep venous thrombosis, pulmonary embolism, and endometrial cancer and two instances of rapidly progressing breast cancer. The serious adverse events reported in the non-HT arm were one instance each of deep venous thrombosis, pulmonary embolism, and cerebrovascular stroke and two instances of rapidly progressing breast cancer. The women with vascular events in the non-HT arm did not use HT.

Discussion

After a median follow-up of 4 years, there was a statistically significantly increased risk of a new breast cancer event in a group of women with a previously treated stage 0–2 breast cancer and without signs of active disease who were randomly assigned to HT for menopausal symptoms as compared with women treated with best symptomatic treatment without hormones. The relative risk—based on a total of 56 events in an intention-to-treat analysis—was 2.4, corresponding to a clinically highly relevant 14% absolute difference in the cumulative incidence of a new breast cancer event at 5 years. Because only 21 women in total were diagnosed with distant metastases (or had died from breast cancer), it is impossible to either rule out or substantiate any effect of HT exposure on the risk of progression to lethal breast cancer. However, if the analysis of time to event

had incorporated all breast cancer events and all deaths together, the results would have been even more unfavorable for the HT arm.

Patient compliance with the recommended treatments was high in the context of HT medication; nevertheless, a total of 12% of patients in the HT arm did not actually take HT, and many women took HT for more than the 2 years stipulated in the protocol. There was a nearly complete monitoring of all original medical records, and only five patients were lost to follow-up. This loss to follow-up was not dependent on randomization arm.

Our study has several potential limitations. Because it was open label and not placebo-controlled, there was a risk for a bias related to possibly more vigorous follow-up and diagnosis of events in the HT arm. However, as indicated by the number of follow-up visits, there were no signs of a more active search for local recurrences or metastases in either group.

Another threat to the validity of our findings is that the interim analysis may have revealed just a random increase in the difference in the rates of new breast cancer events between arms, because if the trial were erroneously terminated early on a random high, all other analyses could have been biased upward. The noninferiority design of the main trial and the design of the interim analyses to detect a difference also make it difficult to interpret both the statistical significance levels of the interim analyses and the final results in a statistically stringent way due to multiple testing. However, it is clear that the accumulation of new breast cancer events continued in the HT arm beyond the first analysis. All women with breast cancer events assigned to the HT arm were exposed to HT, and five of the 17 women in the non-HT arm with a new breast cancer event were also exposed to HT. Half of the women with breast cancer recurrences beyond the recommended 2 years of treatment in the HT arm were exposed to HT close to the time of recurrence. Because the length of HT treatment in the HT arm varied considerably, it is difficult to assess whether the increased risk in the HT arm declined shortly after HT exposure. The change from an HR of 3.5 in our first report to 2.4 in the present report could be attributed to termination of exposure to HT and/or to a random high found in the safety analysis. Nevertheless, the observed relationships between HT exposure and occurrence of new breast cancer events make it unlikely that they are associated only by chance.

It is not surprising that the results from this randomized trial deviate from those in the observational series (2). The majority of the observational studies were not formal studies that could control sufficiently for bias and confounding. Even in the carefully designed observational study from Seattle (12) that studied the risk of breast cancer recurrence following HT among breast cancer survivors and found decreased risk for HT users compared with nonusers (HR = 0.50, 95% CI = 0.30 to 0.85), it was difficult to completely exclude selection bias. An important methodological problem in observational studies is to adjust for the effects of any pretreatment screening for metastases and restaging of those exposed to HT. Furthermore, reliable data on patterns of HT exposure are seldom available in the observational setting. In several of the case series (13–18), one or more of the investigators were also the patients' physicians, which increases the risk that patients do not report back bad outcomes.

Although the Stockholm trial (5) and the HABITS trial were very similar in their basic design, their results are inconsistent. The

Stockholm trial reported in 2005 (5), after a median of 4.1 years of follow-up, a total of 11 new breast cancer events and two breast cancer deaths among 188 women in the HT arm, with 13 new breast cancer events and four breast cancer deaths among 190 women in the non-HT arm. Compliance with protocol treatment was high, with 77% of the women randomly assigned to the HT arm taking HT and only 10% of women in the control group taking HT. In contrast to the HABITS study, however, the relative risk associated with random assignment to the HT arm was not elevated (HR = 0.82, 95% CI = 0.35 to 1.9). In its third and final interim analysis, the DMSC common to both studies found a statistical heterogeneity between the studies ($P = .02$ in a two-sided likelihood ratio test).

Variations in the design of the two studies may account for the discrepant findings. First, there was a higher proportion of women with node-positive breast cancer in the HABITS trial than in the Stockholm trial. Thus, the HABITS trial probably had a higher proportion of women with subclinical disease that could have been stimulated to grow by HT. Second, a higher proportion of the women in the Stockholm study were being treated with tamoxifen, which would theoretically confer protection from breast cancer recurrence. However, our own subset analyses by use of tamoxifen, by nodal status, and by type of HT did not show that any of these differences explain the different outcomes of the two studies. On the other hand, our subset analyses have low precision and power, and true underlying differences cannot be excluded.

A third possible reason for the different results between the HABITS trial and the Stockholm study is that in the HABITS trial the most commonly used HT regimens included a potent testosterone-like progestagen, NETA, either continuously or for at least 10 days of a 28-day cycle. By contrast, the Stockholm study was specifically designed to keep doses of progestagen as low as possible and to use a naturally occurring progesterone, medroxyprogesterone acetate (MPA), instead of NETA. Furthermore, the Stockholm study recommended a sequential regimen for women younger than 55 years and a regimen for older women in which the addition of progesterone to estrogen was given only every third month. If the biology underlying development of a recurrence of breast cancer in the Stockholm and HABITS trials is similar to the biology of induction and promotion of cancer in healthy women, then the difference in the preparations used may explain differences between the outcomes of the two studies. The addition of progestagens in HT has been found to increase the risk of breast cancer (6,7,19–21). There are also indications that NETA is associated with a higher risk of breast cancer than MPA, especially if continuous combined regimens are used (21,22).

In the HABITS trial, the new breast cancer events in the HT arm were mainly local events, and there was no convincing evidence for a higher breast cancer mortality associated with HT exposure. This preponderance of local events, and the lack of influence of HT on breast cancer mortality, may be related to a relatively short follow-up in the HABITS trial, but it may also mirror the clinical experience from HT exposure in women without a previous breast cancer. The evidence from observational studies suggests that HT induces primarily local growth (1), particularly

when progestagens are added to HT (21,23), which was the prevailing type of HT used in this trial.

The results of the HABITS trial indicate a substantial risk for a new breast cancer event among breast cancer survivors using HT. The risk elevation is in line with the evidence from observational studies (1,7) and randomized trials (6) that HT increases the risk of breast cancer in healthy women. Our results further suggest that HT not only induces and promotes breast cancer but may also stimulate the growth of tumor microdeposits in breast cancer survivors. However, the combined evidence from observational studies and the randomized data on risk following HT treatment among breast cancer survivors are conflicting (2). Further data from randomized studies are needed to define both the impact of specific types of HT regimens (eg, type of progestagen included, sequential or combined administration) and accompanying circumstances (eg, a certain type or stage of tumor, HT for a limited time or during tamoxifen treatment) on the risk of recurrence in breast cancer survivors following HT exposure.

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet*. 1997;350(9084):1047–1059.
2. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res*. 2005;7(4):535–540.
3. Marsden J, Whitehead M, A'Hern R, Baum M, Sacks N. Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? *Fertil Steril*. 2000;73(2):292–299.
4. Holmberg L, Anderson H, HABITS Steering and Data Monitoring Committees. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet*. 2004;363(9407):453–455.
5. von Schoultz E, Rutqvist LE; Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm Randomized Trial. *J Natl Cancer Inst*. 2005;97(7):533–535.
6. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288(3):321–333.
7. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419–427.
8. Wyon Y, Lindgren R, Lundeborg T, Hammar M. Effects of acupuncture on climacteric vasomotor symptoms, quality of life and urinary excretion of neuropeptides among postmenopausal women. *Menopause*. 1995;2(1):3–12.
9. ICH Harmonised Tripartite Guideline. *Statistical Principles for Clinical Trials*. §3.3.2. London, UK: European Medicines Agency; 2006. www.emea.europa.eu/pdfs/human/ich/036396en.pdf. Accessed February 27, 2008.
10. Cox DR. Regression analysis and life tables. *J R Stat Soc*. 1972;34:187–220.
11. Kalbfleisch DL, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: John Wiley; 2002:252–258.
12. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst*. 2001;93(10):754–762.
13. Beckmann MW, Jap D, Djahansouzi S, et al. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. *Oncology*. 2001;60(3):199–206.
14. Decker DA, Pettinga JE, VanderVelde N, Huang RR, Kestin L, Burdakin JH. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. *Menopause*. 2003;10(4):277–285.
15. DiSaia P, Brewster W, Ziogas A, Anton-Culver H. Breast cancer survival and hormone replacement therapy: a cohort analysis. *Am J Clin Oncol*. 2000;23(6):541–545.

16. Durna E, Wren B, Heller G, Leader L, Sjoblom P, Eden J. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust.* 2002;177(7):347–351.
17. Marttunen M, Hietanen P, Pyrhonen S, Tiitinen A, Ylikorkala O. A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy. *Maturitas.* 2001;39(3):217–225.
18. Ursic-Vrscaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. *Eur J Surg Oncol.* 1999;25(2):146–151.
19. Chlebowski RT, Hendrix SL, Langer RD, et al.; WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA.* 2003;289(24):3243–3253.
20. WHI Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized trial. *JAMA.* 2004;291(14):1701–1712.
21. Stahlberg C, Tonnes Pedersen A, Lynge E, Ottesen B. Hormone replacement therapy and risk of breast cancer: the role of progestins. *Acta Obstet Gynecol Scand.* 2003;82(7):335–344.
22. Magnusson C, Baron JA, Correia N, Bergström R, Adami HO, Persson I. Breast cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer.* 1999;81(3):339–344.
23. Pike MC, Spicer DV, Dahmouch L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev.* 1993;15(1):17–35.

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